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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MOORE, WILLIAM W	

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/884,456	HOUGHTON ET AL.	
	Examiner	Art Unit	
	WILLIAM W. MOORE	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 30 May 2008 has been entered. No claims were canceled or amended, and claims 27-44 remain in the application.

Double Patenting: Non-Statutory

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 27-44 remain rejected for reasons of record under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 5,371,017.

Claims 27-43 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, 8-12, 14 and 15 of copending application 10/438,313. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant indicates at page 2 of the Response filed 30 May 2008 [Response hereinafter] that (a) terminal disclaimer(s) will be filed to overcome both rejections of record herein upon an indication of allowable subject matter herein, but these rejections must be maintained until and unless an effective terminal disclaimer is filed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-44 remain rejected for reasons of record under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant's arguments at pages 3-15 of the Response have been fully considered but are not persuasive. Applicant now requests an affidavit under 37 CFR 1.104(d)(2) providing facts known to the examiner as to "why the rejection should be maintained". This request is not germane because the rejection is maintained in view of the text of the specification and publications and appellate decisions cited and discussed in the rejection of record and Applicant's arguments. Applicant suggests that the communication mailed 16 November 2007 had not "set out a *prima facie* case of [a] lack of [adequate] written description" because a factual basis must be established by evidence and reasoning to rebut a presumption that the specification's disclosure is adequate. The disclosure must establish Applicant's possession, at the time the disclosure was originally filed, of an invention defined in, e.g., claim 27, as a polynucleotide encoding a "proteolytically active" polypeptide that "consists essentially of an HCV NS3 domain protease" or "an active truncation analog" of an HCV NS3 domain protease".

Claims 28 and 31 provide one statement of what might consist essentially of an HCV NS3 domain protease: the 202 amino acid sequence identically set forth in both SEQ ID NO:1 and SEQ ID NO:65.[1] Neither the specification nor Applicant's argument assert that this 202 amino acid sequence is the least of "active" truncation analogs and whether it is intended to be the least truncation, or the starting point for truncation, the specification nowhere discloses that it is capable of proteolytically cleaving the only substrates purported to be cleaved by a HSV NS3 domain protease: the p300, p500, and p600 fusion constructs of Examples 4 and 5.[2] Thus

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[1] The undecapeptide of SEQ ID NO:63 and the nonapeptide of SEQ ID NO:64 described by, respectively, claims 29 and 30, are far to small to retain proteolytic activity. Both peptides reside within SEQ ID NO:65.

[2] The specification suggests, at pages 19-21, that peptides comprising at least two consecutive arginines, or the three particular peptides set forth in SEQ IDs NOs:36, 88, and 89, or the HCV polyprotein, are all potential substrates but does not disclose the structure of a HCV NS3

examples 4 and 5 suggest that an HCV NS3 domain protease might consist essentially of the 686 amino acid sequence set forth in SEQ ID NO:70. This is the greatest portion of the HSV polyprotein Applicant fused to human superoxide dismutase [HSOD] to provide the "P600" fusion polypeptide the amino acid sequence of which is set forth in SEQ ID NO:86. Applicant asserts at page 6 of the Response that this particular, larger, structure disclosed in the specification and comprising SEQ ID NO:65 has an "NS2/NS3" proteolytic activity, but the specification does not contemplate such activity. "While one does not need to have carried out one's invention before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. §112. *Fiers v. Revel v. Sugano,* 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). The NS2/NS3 autocatalytic metalloprotease activity takes place at a region of the HCV polyprotein that is absent from SEQ ID NO:70, a fact established by the record of argument in this application, and was discovered after the specification was originally filed, thus could not reasonably considered by the artisan to have been in Applicant's possession at the time the specification was originally filed. Applicant also asserts at page 6 of the Response that Examples 10 and 11 disclose an NS3 serine protease activity but these Examples do not discuss proteolysis or NS3 domain serine protease activity. The "test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the Inventor had possession at that time of the . . . claimed subject matter", *In re Kaslow*, 217 USPQ 1089, 1096 (Fed. Cir. 1983).

The factual inquiries presented are twofold: Does the specification disclose that the structure defined by SEQ ID NO:65 meets the functional limitation, serine protease activity, of claim 27? If it does not, does the specification disclose some other, more extensive, structure adequate to reasonably convey to the artisan that Applicant had possession of a NS3 domain polypeptide with serine protease activity according to claim 27? At pages 7-8 of the Response Applicant asserts that several publications made five or more years after the specification was originally filed indicate that that SEQ ID NO:65 might function, alone, as a serine protease, but only Sardana et al., made of record by the examiner, has been cited in this application and none of the HCV polyprotein regions that Sardana et al. or Eckart et al., previously discussed in this application, report to be substrates cleaved by an HCV NS3 serine protease are disclosed or suggested in the specification and all are absent from the expression constructs of Examples 4

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domain protease that cleaves at two consecutive arginines, cleaves the peptides set forth in SEQ IDs NOs:36, 88, and 89 or that can independently cleave any particular portion of the HCV polypeptide.

and 5. The specification thus fails to disclose that SEQ ID NO:65 has a serine protease activity and fails to disclose any region of the HCV polyprotein that could serve as substrate according to Bartenschlager et al., 1994, of record in this application and discussed in the communication mailed 16 November 2007, to be present in a fusion polypeptide purportedly cleaved, at least by SEQ ID NO:70, in Example 5.

Taking up the issue of larger regions of an HCV NS3 domain disclosed in the fusion polypeptides of Examples 4 and 5 of the specification, Applicant first misconstrues, at page 6 of the Response, a discussion in the communication mailed 16 November 2007. The paragraph that spans pages 5 and 6 in that communication speaks for itself, arguing against what Applicant misinterprets as a concession. None of the P600, P500, or P300 fusion polypeptides comprise substrate regions later determined by others to be recognized the NS3 domain. None extends as far as the border between the NS3 domain and the NS4 domain, i.e., the NS3/NS4A cleavage site reported by Bartenschlager et al. in the paragraph that spans the left and right columns at page 5050. Thus no polynucleotide disclosed in the specification comprises a coding sequence that could have specified a NS3 domain region having serine protease activity on, and cleaving, the only substrates the specification's Example 5 indicates to be cleaved, the fusion polypeptides themselves. Applicant's following argument in the Response, premised on a HCV NS/23 metalloprotease activity, is similarly unpersuasive, where (i) it is not a serine protease activity, (ii) there is no disclosure or suggestion of this activity in the specification, and (iii) there is no NS2/NS3 cleavage site present in any of the fusion polypeptides. Applicant's final argument, that the presence of HSOD as an amino-proximal fusion partner reconstitutes a kind of NS2/NS3 autocatalytic cleavage, is also unpersuasive because the mass of the cleavage fragment produced does not indicate that the cleavage was produced by a HCV NS2/3 autocatalytic activity and such proteolytic activity, when it occurs in the HCV polyprotein, is not a serine protease activity. The rejection of record is therefore maintained.

Claims 27-44 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably enable the preparation of polynucleotides that encode proteins, including the P600, P500, P300 and P190 proteins, that comprise an HCV-specific protease activity, or generic versions thereof, or active truncation analogs thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant's arguments at pages 14-20 of the Response filed 30 May 2008 have been fully considered but are not persuasive. Applicant suggests at page 15 of the Response that it is necessary to provide a reason to doubt the objective truth of the statements in the specification.

Enablement must be provided for the full scope of the claims, all which require that an encoded polypeptide have serine protease activity, thus Applicant's initial argument, that the specification should be considered to enable a NS2/3 protease, is inappropriate where only the subsequent discoveries by others established this to be an autoproteolytic metalloprotease activity. In addition, where there is not a hint in the specification that such an activity exists, there is no enabling guidance for practicing an invention without undue experimentation. The guidance provided by the specification is a key factor in determining whether or not a disclosure can enable the breadth of the claims and whether or not "undue experimentation" would be required to make and use an invention commensurate in scope with the claims. The CCPA, the precursor of the Court of Appeals for the Federal Circuit, determined that a reasonable correlation must exist between the scope asserted in the claimed subject matter and the scope of the guidance the specification provides. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 25 (CCPA 1970) (emphases supplied). The Federal Circuit approved the standard set by the CCPA in *Genentech, Inc. v. Novo-Nordisk A/S*, 42 USPQ2d 1001 (Fed. Cir. 1997).

Applicant also argues at pages 17-20 of the Response that the absence of disclosure of any substrate actually cleaved by a HCV NS3 domain serine protease creates no impediment to experimentation that might somehow enable the preparation and use of some or all of the NS3 domain as a serine protease where an artisan could also conduct experimentation to find a substrate. Applicant does not explicitly suggest that the encoded SEQ ID NO:70 should replace the P190, P500, and P600 fusion polypeptides or become a fusion partner with hSOD in a fusion polypeptide of the claims. Applicant suggests, however, that the specification's indication that the HCV polyprotein is a substrate is adequate to begin the search for substrates. For the reasons set forth in the preceding discussion of the specification's lack of an adequate written disclosure there is no enabling step in the only cleavage that is taught by the specification where no HCV polyprotein region actually cleaved by a HCV protease is present in the P600, P500 or P300 fusion polypeptides, not even the NS3/4 cleavage site. Thus no serine protease cleavage at the NS3/4 boundary could be detected that might permit the artisan to screen suitable substrates to then establish a structure beyond that of SEQ ID NO:65 that serves as a serine protease. The only particular substrates the specification proposes, at pages 19-21, are not substrates of the NS3 domain serine protease of SEQ ID NO:65. See pages 8 and 9 of the communication mailed 30 November 2007. There is no guidance in the specification as to what more might be required beyond the amino acid sequence of SEQ ID NO:65 to locate the sequence of NS4A cofactor, a cofactor that is not present in SEQ ID NO:65 which was discovered in the art well after the date for the disclosure of the specification herein, that could

bring about cleavage of the native polyprotein. Because the scope of guidance provided by the specification does not indicate the direction the artisan might take to begin the next, necessary, process of experimentation, the rejection of record is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. § 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27-44 remain rejected for reasons of record under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's arguments at pages 20-24 of the Response have been fully considered but are not deemed to be persuasive to overcome the rejection of record. Applicant suggests that the recitation "HCV proteolytic polypeptide" clearly define the metes and bounds of the intended subject matter because the artisan can distinguish that which is infringed from that which is not infringed if a polypeptide (i) has some origin in a HCV polyprotein and (ii) has protease activity. Yet the independent claims 27 and 37 provide no basis for the artisan to distinguish between a "HCV NS3 domain protease" and a "truncation analog" of a HCV NS3 domain protease that is proteolytically active. Because there is no starting point that allows a distinction to be made, other than an entire HCV polyprotein, Applicant appears to argue that any polynucleotide encoding all or part of an HCV polyprotein, and any polynucleotide derived from the HCV viral genome but differing to an indeterminable extent from a disclosed HCV nucleic acid sequence, should be considered by the artisan to be the invention, if it can be altered to have a protease activity. Where there is no starting point delineating a structure that permits the artisan and the public to distinguish between polynucleotides that need have no particular relationship to a disclosed polynucleotide and that encode any kind of protease that will cleave HCV polyproteins anywhere, whether or not the site is actually recognized by a native HCV NS3 domain serine protease, the metes and bounds of the intended subject matter are clearly indefinite. Until and unless the claims are amended to provide a definite basis for distinguishing a first "HCV NS3 domain protease", and all lesser truncation analogs, from other proteases, the rejection of record of claims 27-44 must sustained.

Applicant addresses the separate rejection of record of claims 27-31 as indefinite in view of claim 27's phrase, "consists essentially of" at pages 23 and 24 of the Response. Applicant now cites *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1240-41 (Fed. Cir. 2003) for the proposition that a percentage composition of metal ions in a coating informs the construction of a claim to an

informational molecule. The citation is inapposite where the percentages of the atoms that comprise any region of a HCV viral genome can readily be determined but cannot indicate the information embodied in the structures that provide the function of an encoded and expressed polypeptide. Each rejected claim necessarily describes a polymer within which each nucleotide is covalently bonded to at least one other nucleotide, and a resulting polynucleotide can have no physically separate, lesser, component, thus cannot "consist essentially of" one component. Thus the rejection of record of claims 27-31 is sustained.

Conclusion

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 571.272.0933 and whose

FAX number is 571.273.0933. The examiner can normally be reached Monday through Friday between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Primary Examiner, Dr. Kathleen Kerr Bragdon, can be reached at 571.272.0931. The official FAX number for all communications for the organization where this application or proceeding is assigned is 571.273.8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571.272.1600.

/William W. Moore/
30 July 2008

/Kathleen Kerr Bragdon/
Supervisory Patent Examiner, Art Unit 1656